

Retroperitoneal liposarcoma, outcome of a tertiary referral center from Egypt

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ABSTRACT

Background: Retroperitoneal liposarcoma is the commonest adult's soft tissue sarcoma. It is a slowly growing tumor commonly presents >10cm & at advanced stage. CT is the preferred diagnostic tool. Biopsy is still controversial. Surgery with clear margins is the gold standard for management. Certain situations permit aggressive surgery without R0 resection resulting in inevitable recurrences requiring repeated resection again with improved DFS & OS. CTH protocols are given individually to high grade, failed R0 resections, recurrent & metastatic cases. Well differentiated type carries low metastatic potential but high local recurrence rate with about 90% 5-years OS. Undifferentiated type beside its high local recurrence rate carries high metastatic potential (lungs) still low than expected (10–15%). Large tumor volume & wide anatomical extents causes' poor outcome & morbidities with RT. Eventually repeated local recurrences become impossible for surgery with resultant mortality from its local destructive effects. **Aims:** To study clinicopathological features of all cases of RPLS, presentation, types, prognostic factors, management (surgery, RT & CTH) & outcome (DFS & OS). **Materials & Methods:** A single institution combined prospective & retrospective analysis of all cases presented to NCI-Cairo University with primary non-metastatic RPLS over period of 8 years from Jan 2012 to Dec 2019. Retrospective study is from Jan 2012 until Dec 2016 & prospective from Jan 2017 until Dec 2019. 52 cases were included. Data collected then analyzed. **Results:** Mean age was (50.6 years) with males/females ratio 1.2. Tumor sizes ranged (13-43cm) mean & median sizes 11.2 & 9cm respectively. Most tumors sized <20cm (30 cases, 57.6%). Median tumor burden (39cm) ranging (21-89cm). Commonest presentation was distension (31 cases, 57.6%) with mass palpated intra abdominally (41 cases, 78.8%). Preoperative image guided biopsy used only in (29 cases, 55.7%). PET-CT used (21 cases, 40.3%) mainly on follow-up. Median hospital stay was (11 days) ranging (8-31 days). Well differentiated type predominated (31 cases, 59.6%). High grade (III) found in (17 cases, 32.6%). Clear margins obtained in (31 cases, 59.6%) with nearby organs resection in (35 cases 67.3%). Commonest postoperative morbidity was SSI (29 cases, 55.7%). Postoperative mortality was in (6 cases, 11.5%). Postoperative CTH (38 cases, 73%) given to all high-grade, non R0 resection & as palliation in recurrent & metastatic cases (35 cases, 67.3%). Post-operative RT given (15 cases, 28.9%) mainly for non R0 resections unfit for CTH. Median



follow up time was (63 months) ranging (0.06-9.31 years). OS at 1, 3 & 5 years were 96.2%, 72.4% & 43.9% respectively while corresponding DFS were 68.7%, 30.8% & 17% respectively.

Keywords: Retroperitoneal liposarcoma, Outcome, NCI, Cairo University.

1. INTRODUCTION

Soft tissue sarcomas (STSs) are rare tumors accounting for 1% of malignancies. They can occur anywhere including the retroperitoneum. About 30 % of tumors arising in retroperitoneal space are STS. Commonest of them is liposarcoma (RPLS) (40%) which is also commonest adult STS (20%). It is worth mentioning that some types of liposarcoma shows specific predilection to certain sites; myxoid/round cell & pleomorphic types occurs mainly in extremities, while well differentiated & the undifferentiated types have great affinity for the retroperitoneum (Liles et al., 2009).

RPLS is a slowly growing tumor usually present at advanced stage. It is often silent & reaches larger sizes (>10cm) carrying dismal prognosis compared to other retroperitoneal sarcomas. Histologically, four main types are present based on morphology & cytogenic abnormalities (well-differentiated, undifferentiated, myxoid/round cell & pleomorphic types). Cell grading & degree of differentiation are the most important factors affecting outcome of treatment & anticipates their prognosis (Singer et al., 2003). The undifferentiated type usually carries pathological challenge as it carries multiple different histologic features making it difficult for diagnosis. It resembles myxofibrosarcoma, malignant fibrous histiocytoma (MFH) or pleomorphic sarcoma. Frequently presents advanced & late compared to other RPLSs (named "silent killer") (Shibata et al., 2001).

CT scan is the radiological investigation frequently used in evaluation due to the fat character of tumor. It identifies tumor site & relations, also clarify secondaries in liver, peritoneal cavity or skeleton. Often it is difficult to obtain high-quality MRI cuts due to frequent motion artifacts. CT is less sensitive to these artifacts (Heslin & Smith, 1999). Preoperative biopsy is controversial. Some recommend surgery next to radiological diagnosis of retroperitoneal mass with high fat content. Others advocate preoperative pathology as it may change treatment plans [gastrointestinal stromal tumors (GIST), germ cell tumors or lymphomas] appear as retroperitoneal masses with some fat content. In such situations, imatinib (Gleevec) or CTH is used initially instead of surgery (Neuhaus et al., 2005).

Surgery with clear margins is the gold standard for treatment. This may not be easy especially in well differentiated types with extensive fat differentiation where margins cannot be clearly demarcated from normal retroperitoneal fat. This usually justifies major organ resections with dramatic deterioration of life quality following these resections (Lahat et al., 2008). For high grade types (undifferentiated, myxoid/round cell & pleomorphic), combined regimens including adriamycin & ifosfamide can give complete response (CR) & partial response (PR) in 10% & 50% respectively, with limited improvement in overall survival (OS). There is evidence of differential response & sensitivity to chemotherapy (CTH) based on the liposarcoma type. This response may also be related to the anatomic site where extremity liposarcoma responds better than other sites. In metastatic disease, traditional regimens containing doxorubicin/ifosfamide or gemcitabine/docetaxel result in response rates of 25 to 35% and survival of 12 to 18 months (Pervaiz et al. 2008).

On the contrary of other retroperitoneal STS, RPLS in certain situations may permits aggressive surgery without complete resections resulting in inevitable recurrences that require repeated resection again & again. This is because RPLS carries very low systemic failure rate (7%) compared to other retroperitoneal STS. A study by Shibata et al, (2001) showed that a longer survival was obtained with debulking RPLS compared to others underwent biopsy only. Moreover, 75% of those performed debulking surgeries gained long & effective palliation (Shibata et al., 2001; Gronchi et al., 2004). In the retroperitoneum, the role of adjuvant radiation therapy (RT) is evolving but still a matter of controversy. Some studies had described favourable overall survival (OS) & local control rates when introducing adjuvant RT as compared to surgery alone. RT may be delivered with acceptable toxicity, particularly with intensity-modulated radiation therapy (IMRT) preoperative. Preoperative RT may be preferred for the benefits of displacement of bowel out of the radiation therapy field by the *in situ* tumor, defining more accurate tumor volume, reducing intra-operative tumor seeding & delivering an overall smaller radiation dose. Although this there is no universal agreement for the delivery of RT preoperative as a result of the potential added complications at surgery (Pisters et al., 2003; Pawlik et al., 2006).

The well differentiated RPLS have minimal metastatic potential, although it carries very high local recurrence rate with 5-years OS nearly 90%. Mortality usually results from repeated multiple recurrences causing direct pressure on critical nearby organs. On the other side of the road, undifferentiated type carries critical local effects besides its high metastatic potential (mainly lungs).

Despite being high grade with undifferentiated morphology, still undifferentiated RPLS carries significant lower systemic failure rate (10–15%) than one would expect, with 5-years OS approaching 75% (Ferrario & Karakousis, 2003; Milone et al., 2011).

The myxoid/round cell type is a variant based on the extent of round cell component for its histologic grading. In a study from Memorial Sloan-Kettering Cancer Center (MSKCC), cases with low-grade myxoid/round cell (<5% round cell areas) had 5-years OS nearly 90%, while high-grade myxoid/round cell (>5% round cells areas) had 5-years OS about 60%. The pleomorphic RPLS is the least common type, usually diagnosed after exclusion of other types; they are high grade tumors with aggressive metastatic potential & estimated 5-years OS about 30% (Antonescu et al., 2001; Gebhard et al., 2002).

In low grade well differentiated types, CTH has limited role due to low mitotic activity of these tumors. The only implementation for CTH is for high grade types (undifferentiated, myxoid/round cell & pleomorphic) & recurrent/metastatic cases unfeasible for surgical resection. The large tumor volume & wide anatomical extent is the main cause of poor outcome & multiple major morbidities with RT therefore, some authors recommend RT only for patients with R1 or R2 resections unfit for CTH (Raut & Pisters, 2006). Frequent local recurrences eventually become impossible for control. At the end mortality results from its local destructive effects. Despite aggressive surgeries, 5 years OS does not exceed 50% in most series due to poor knowledge about biology of RPLS & its molecular alteration. This needs further work towards targeted agents that target specific translocation or amplification products giving a chance & hope for complete cure (Thomas et al., 2009).

Aim of work

This work aims to study clinicopathological features of all cases with RPLS, clinical features, histological subtypes, prognostic factors, management including surgery, RT, CTH & outcome (DFS & OS).

2. PATIENTS AND METHODS

This is single institution combined prospective & retrospective descriptive analysis of all cases with primary non-metastatic RPLS candidate for surgery presented to NCI-Cairo university over a period of 8 years from Jan 2012 to Dec 2019. Retrospective analysis was from Jan 2012 until Dec 2016 & prospective analysis from Jan 2017 until Dec 2019. 52 cases were included. Data collected from patients' archive at statistical department. Data included demography (age & sex), tumor characters (type, grade, stage), treatment received (surgery, CTH, RT), surgical morbidity, mortality occurred & outcomes (OS & DFS).

Histology at presentation were classified into 4 main types (Well-differentiated, Undifferentiated, Myxoid/Round cell tumor & Pleomorphic) according to WHO classification & graded as I, II or III according to French Federation of Cancer Centers Sarcoma Group grading systems. Margins were considered free microscopically if no tumor within 1 mm or more of inked surgical margin was found. Tumor burden determined by adding sum of 3 maximum diameters & tumor size was defined as the maximum diameter of the tumor.

Treatment failures were classified into local recurrence & distant metastasis. Patients were followed up at 3-month intervals for 1st year then 6-monthly thereafter. Data obtained during follow-up included state of disease (alive with or without disease, dead of disease or treatment, dead of other causes). CT, MRI or PET-CT was performed at follow up visit to exclude recurrences. CTH was given to high grade, non R0 resections, metastatic or recurrent diseases. RT was given postoperatively for palliation. Ethical clearance for the conduction of this study was obtained from our institute ethical committee.

3. RESULTS

This cohort included 52 patients with primary non-metastatic RPLS candidate for surgical resection with curative intent. Mean age at presentation was 50.6 years with median of 54.1 years ranging (33–67 years). 28 cases (53.8%) were males while (24 cases, 46.1%) were females with males/females ratio of 1.2 (table 1). Commonest presentation was abdominal distension (31 cases, 26.9%). Other presentations resulted from pressure on surrounding vessels & viscera or their local invasion. Bilateral LL edema, urinary (frequency, dysuria or retention), GIT (obstruction, constipation, dyspepsia), generalized abdominal pain or haemorrhage were among most striking symptoms. By clinical examination, a mass is usually clearly palpated intraabdominally in most of our cases (41 cases, 78.8%).

The commonest radiological investigation used was CT scanning with contrast (34 cases, 65.3%). Preoperative image guided biopsy was not used in all cases (only 29 cases, 55.7%). PET CT main usage was during follow up visits (21 cases, 40.3%). Median hospital stay was 11 days ranging (8–31 days). Tumors ranged in sizes (13–43 cm). Mean & median sizes were 11.2 & 9 cm respectively. Most tumors were <20 cm (30 cases, 57.6%). The median tumor burden was 39 cm ranging (21–89 cm). Tumor sizes did not show statistical significant difference among males & females (means of 11.4 & 11.5 cm, respectively; p-value=0.91). Also, sizes

did not show any significance among patients <40 years & those >40 years (means of 9.57 and 10.43 cm, respectively; $p = 0.71$). Following surgical resection, well differentiated (sclerosing) RPLS was the commonest pathology (31 cases, 59.6%), (12 cases, 23.1%) were myxoid/round cell tumors, (6 cases, 11.5%) were undifferentiated & (3 cases, 5.8%) showed pleomorphic type. Concerning grading (27 cases, 51.9%) were grade I, (8 cases, 15.3%) were grade II while high grade (grade III) found in (17 cases, 32.6%).

Clear post-operative margins obtained in (31 cases, 59.6%) while margins were involved in (21 cases, 40.3%). The need for nearby organ resection (liver, colon, small bowel, part of psoas major muscle, tail of pancreas, spleen or part of anterior abdominal wall) to achieve clear gross margins was justified in (35 cases 67.3%). However, commonest single organ needed to be resected was the kidney (29 cases, 55.7%). As regard postoperative treatment; CTH was given to (38 cases, 73%) High grade was (17 cases, 32.7%) or non R0 resection (21 cases, 40.3%); while RT was given only to (15 cases, 28.9%) mainly as a palliation.

Median follow uptime was 63 months ranging (0.06-9.31years). Operative morbidity & mortality were those occurring within one month after surgery. Postoperative mortality occurred in (6 cases, 11.5%). Commonest postoperative morbidity was surgical site infection (SSI) (29 cases, 55.7%). Others morbidities were; wound dehiscence, reactionary hemorrhage needed re-surgery, pneumonia, septicemia, intra-abdominal abscess, intestinal fistula, DVT & pulmonary embolism) (table 1).

Table 1 Clinicopathologic characteristics of our patients (52 cases, 100%)	
Age:	
Mean (50.6 ys, SD 12.1), median (54.1 ys), range (33-67ys)	
<40 ys	39 cases, 75%
> 40 ys	13 cases, 25%
Sex: males to females ratio = 1.2	
Males	28 cases, 53.8 %
Females	24 cases, 46.2 %
Main symptomatology:	
Abdominal mass	23 cases, 44.2%
Bilateral LL swelling	11 cases, 21.2%
Urinary	9 cases, 17.3%
GIT	5 cases, 9.6%
Pain	3 cases, 5.8%
Bleeding	1 case, 1.9%
Main investigations:	
CT scanning	34 cases, 65.3%
MRI	18 cases, 34.6%
Image guided biopsy	29 cases, 55.7%
PET CT (on follow-up)	21 cases, 40.3%
Tumor size:	
Mean (11.2cm), Median (9cm) & ranging(13-43cm)	
< 20 cm	30 cases, 57.6%
>20 cm	22 cases, 42.4%
Histology:	
Well differentiated	31 cases, 59.6%
Myxoid/round cell	12 cases, 23.1%
Undifferentiated	6 cases, 11.5%
Pleomorphic	3 cases, 5.8%
Tumor Grade:	
Grade I	27 cases, 51.9%
Grade II	8 cases, 15.4%
Grade III (high grade)	17 cases, 32.7%
Margins:	
Negative Margins	31 cases, 59.6%
Positive Microscopic	13 cases, 25%

Positive Gross	8 cases, 15.4%
Resection of nearby organs:	
Yes	35 cases, 67.3%
No	17 cases, 32.7%
Nephrectomy only	29 cases, 55.7%
Postoperative complications: (> one complication may present in same patient)	
Surgical site infection (SSI)	29 cases, 55.7%
Wound dehiscence	18 cases, 34.6%
Pneumonia	11 cases, 21.1%
Secondary hemorrhage	7 cases, 13.4%
Septicemia	6 cases, 11.5%
Intra-abdominal abscess	5 cases, 9.6%
Enterocutaneous fistula	4 cases, 7.6%
DVT	3 cases, 5.7%
Pulmonary embolism	2 cases, 3.8%
Non-surgical treatment:	
Post-operative RT	15 cases, 28.9%
Post-operative CTH	38 cases, 73%

Survival

Table 2 & 3 shows survival variables with OS & DFS rates. OS at 1, 3 & 5 years were 96.2%, 72.4% & 43.9% respectively while corresponding DFS were 68.7%, 30.8% & 17% respectively.

Table 2 Overall Survival %							
Factor	No	1y	3 ys	5 ys	8 ys	Median	P-value
All	52 cases, 100%	96.2	72.4	43.9	NA	15.1	57.2
Age:							
< 40 years	39 cases, 75%	97.8	71.5	38.9	22.9	57.2	0.89
> 40 years	13 cases, 25%	91.7	60.1	54.6	NA	89.7	
Gender:							
Males	28 cases, 53.8%	94.6	71	44.4	17.8	58.3	0.81
Females	24 cases, 46.2%	95.8	73	43.7	20.4	57.2	
Grade:							
I	27 cases, 51.9%	80	60	NA	NA	58.2	0.85
II	8 cases, 15.4%	94.2	73.2	46.8	15.1	42.1	
III	17 cases, 32.6%	92.3	57.7	24	NA	57.2	
Histology:							
Well differentiated	31 cases, 59.6%	94.7	39.9	29	9.6	40.1	0.09
Myxoid/round cell	12 cases, 23.1%	92	39.7	27	5	27.6	
Undifferentiated	6 cases, 11.5%	63	22	16	NA	13	
Pleomorphic	3 cases, 5.8%	27	13	7	NA	NA	
Margin:							
Negative Margins	31 cases, 59.6%	95.2	73.6	58.6	NA	83.2	0.031
Positive	13 cases, 25%	94.6	72.9	44.3	NA	55.2	
Microscopic							
Positive gross	8 cases, 15.4%	91.3	69.7	33.3	NA	57.2	0.038
Size:							
< 20 cm	30 cases, 57.6%	93.8	79.5	44.3	20.3	77.5	0.038

> 20 cm	22 cases, 42.4%	91.4	55	31	9.7	42.1	
Organ resection:							
Yes	35 cases, 67.3%	97.5	74.5	45.2	24.5	58.3	
No	17 cases, 32.7%	86.7	61.3	40.9	NA	77.4	0.083
Nephrectomy only	29 cases, 55.7%	87.5	62.5	18.8	NA	39.9	
CTH given							
Yes	38 cases, 73%	95.1	76.6	43.7	33.2	58.2	
No	14 cases, 27%	95.2	65.7	40.5	11.9	55.1	0.067
RT given							
No	37 cases, 71.1%	97.4	79.7	52.6	22.3	69.1	
Yes	15 cases, 28.9%	85.2	49.1	21.4	NA	36.1	0.071

Concerning OS analysis; our work showed only sizes & surgical margins showed significance. Sizes <20cm versus those >20 cm were significant with improved OS (44.3% versus 31% at 5 years, respectively; $p=0.038$). -ve margins were associated with significant improvement of OS rates over +ve microscopic or +ve gross margins (58.7% versus 45.3% versus 33.4% at 5 years, respectively; $p = 0.031$). Other variables as histological type, contagious organ resection, RTH & CTH showed only border line significance. Differentiated type showed border line OS improvement over myxoid/round cell, undifferentiated & pleomorphic types respectively (29% versus 27% versus 16% versus 7% at 5 years; $p= 0.09$). Contagious organ resection was also associated with border line improvement of OS rates for those received organ resection versus those who did not (45.3% versus 36.7% at 5 years respectively; $p=0.083$). Again, patients received RTH vs those did not & those received CTH versus those who did not showed both border line OS improvement (52.6% versus 21.4% at 5 years; $p=0.071$) & (43.7% versus 40.5% at 5 years; $p=0.097$) respectively. Patient's age and gender & grade did not show any influence on OS rates (table 2).

Table 3 Disease Free Survival %							
Factor	No	1 y	3 yr	5 yr	8 yrs	Median	P-value
All	52 cases, 100%	68.7	30.8	17	NA	20.1	20.1
Age:							
< 40 years	39 cases, 75%	69.6	28.9	14.1	10.6	19.3	
> 40 years	13 cases, 25%	60.8	26.2	13.1	NA	18.9	0.97
Gender:							
Males	28 cases, 53.8%	65.5	29.1	14.4	NA	20.3	
Females	24 cases, 46.2%	70.2	32.8	12.3	NA	19.5	0.89
Grade:							
I	27 cases, 51.9%	60	20	NA	NA	20.3	
II	8 cases, 15.4%	69.1	32.8	18.5	13.9	20.8	0.51
III	17 cases, 32.6%	53.8	23.1	11.5	NA	15.6	
Histology:							
Well differentiated	31 cases, 59.6%	71.6	43.3	18.2	9.8	21.1	
Myxoid/round cell	12 cases, 23.1%	61.9	32.5	17	6	14.6	
Undifferentiated	6 cases, 11.5%	37.5	12.5	NA	NA	8.1	0.038
Pleomorphic	3 cases, 5.8%	22.9	10.8	NA	NA	7.3	
Margin:							
Negative Margins	31 cases, 59.6%	68	39.2	NA	NA	20.8	
Positive Microscopic	13 cases, 25%	64.9	24.2	18.8	NA	18.9	0.031
Positive Gross	8 cases, 15.4%	57.1	23.4	10.8	NA	21.4	
Size:							
< 20 cm	30 cases, 57.6%	70.8	38.8	14.7	9.2	25.5	
> 20 cm	22 cases, 42.4%	54.3	12.9	3.2	NA	13.2	0.49
Organ resection:							

Yes	35 cases, 67.3%	87.6	49.4	22.6	14.2	20.1	0.022
No	17 cases, 32.7%	68	30	16.7	NA	18.2	
Nephrectomy only	29 cases, 55.7%	66.7	NA	NA	NA	NA	
CTH given:							
Yes	38 cases, 73%	74.9	34.4	20.4	13.6	20.3	0.035
No	14 cases, 27%	64	29.5	11.2	7.5	19.3	
RT given:							
No	37 cases, 71.1%	75.3	37.7	19.1	11.9	22.1	0.2
Yes	15 cases, 28.9%	44.4	9.4	6.7	NA	9.9	

For DFS analysis; size, histology, margins, organ resection & CTH given were showed significance. Tumors sizes <20 cm had better DFS than those with tumors >20 cm (38.8% versus 12.9%, 14.7% versus 3.2% at 3 & 5 years respectively; $p=0.049$). Well differentiated type was associated with significant improved DFS over myxoid/round cell, undifferentiated & pleomorphic subtypes (43.3% versus 32.5%, versus 12.5%, versus 10.8 at 3 years respectively; $p=0.038$). Negative margins versus +ve microscopic & +ve gross margins were associated with significant improved DFS (39.2% versus 24.2% versus 23.4% at 3 years, respectively; $p=0.031$). Those received organ resection were associated with significant improved DFS versus those who did not (22.6% versus 16.7% at 5 years respectively; $p=0.022$). Finally, patients received CTH showed significant DFS benefit over those who did not (19.1% versus 6.7% at 5 years; $p=0.02$), although similar influence was not obtained on OS. Patients age, sex, grade & RT given did not show any significant influence on DFS (table 3).

Patterns of failure: Relapse occurred in (35 cases, 67.3%); 8 cases (15.3%) with local failure, 17 cases (32.6%) with systemic failure & 10 cases (28.8%) both local & systemic. Local control rates at 1, 3 & 5 years were 68.7%, 30.8% & 17% respectively. Distant metastasis free survival rates at 1, 3 & 5 years were 96.2%, 72.4% & 43.9% respectively. Time to local failure ranged (2.97-96.33 months), with median (43.3 months) while time to distant failure ranged (2.28-98.96 months) with median (32.6 months). Distant metastases occurred in lungs (28 cases, 53.8%), bone (7 cases, 13.4%) & peritoneum (4 cases, 7.6%) respectively (figure 1, 2 and 3).

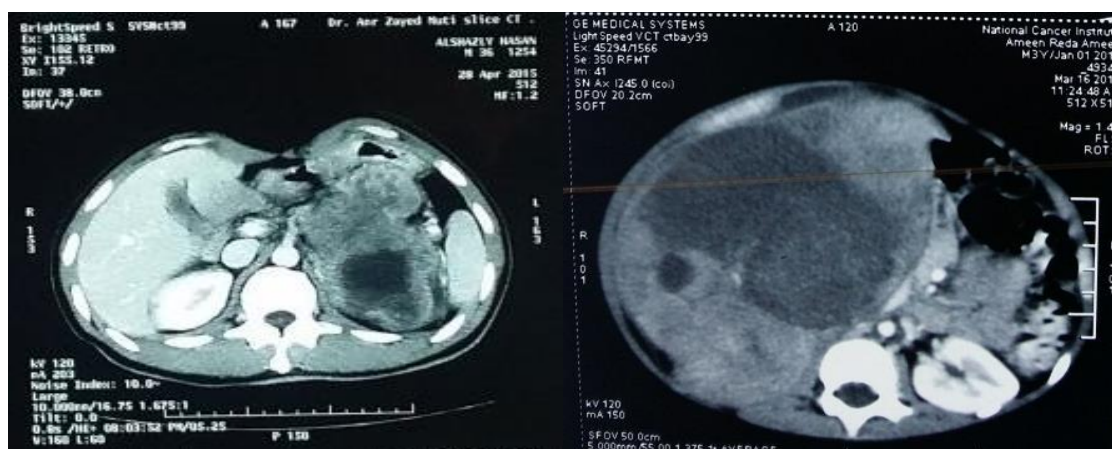


Figure 1 CT scan (axial) of two cases with Lt & Rt RPLS invading correspondent kidney.

4. DISCUSSION

Liposarcoma is the commonest mesenchymal retroperitoneal tumor. It carries a challenge for its diagnosis, behavior prediction & treatment especially when recurrences occur which is inevitable. RPLS lacks pathognomonic symptomatology & often attains huge sizes before bringing patients to clinics. In our work, abdominal distension (31 cases, 59.0%) was commonest presentation with mass palpated in (41 cases, 78.8%). Tumors >20 cm occurred in (22 cases, 42.4%). Our mean & median tumor sizes were 11.2 & 9 cm respectively while median tumor burden was 39 cm (Na et al., 2012). As a result of the disappointing results of RT & CTH, complete surgical resection with clear margins of surrounding organs is the only way to achieve cure. Few studies supported improved DFS rates with adjuvant RT compared to surgery alone. In our work, RT or CTH was given postoperatively only in high grade tumors, non R0 resection, recurrent or metastatic cases. Postoperative RT was given to (15 cases, 28.9%) while CTH was given to (38 cases, 73%) with significant results over DFS obtained only with adjuvant CTH only. Neoadjuvant protocols were not used in this cohort (Sampath et al., 2010).

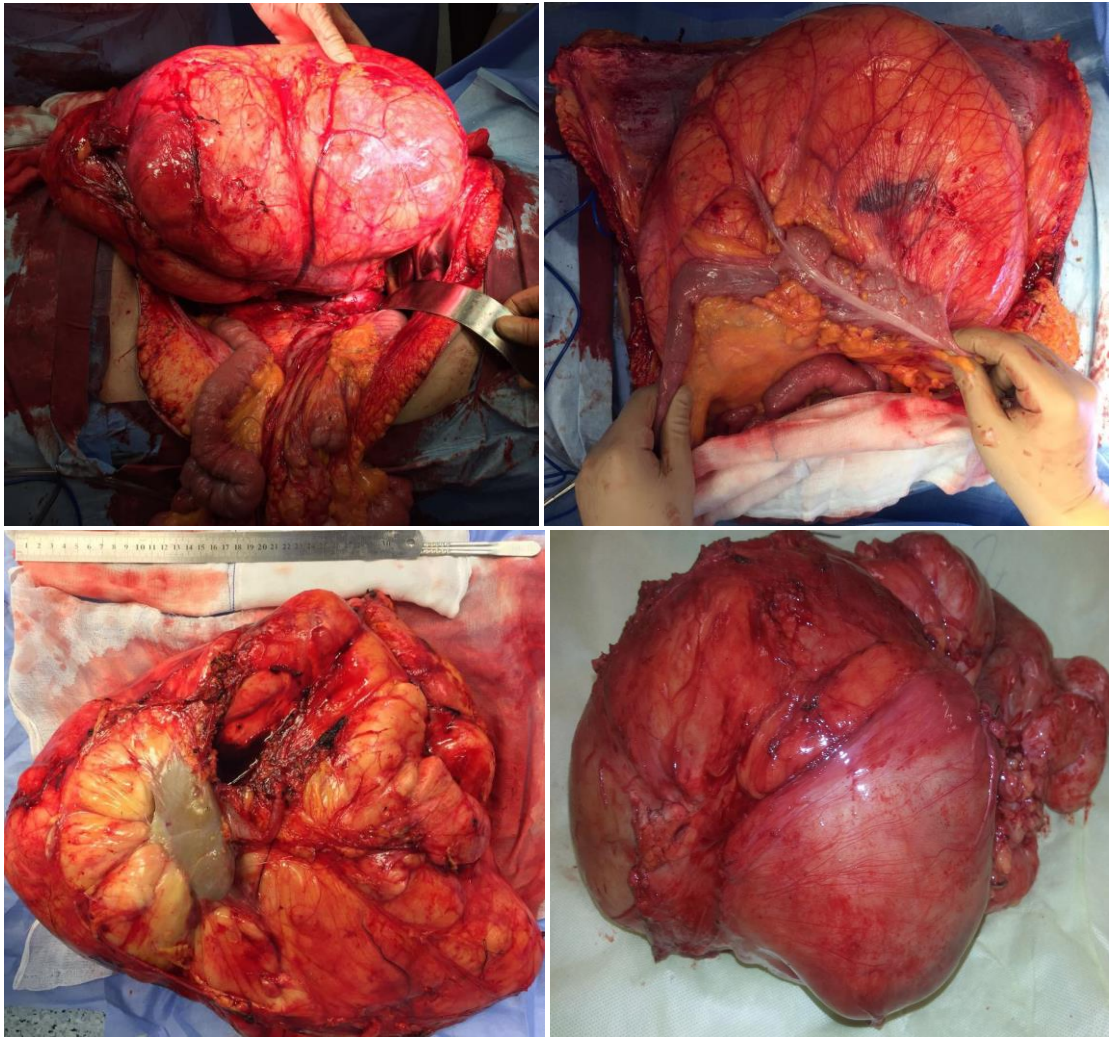


Figure 2 intraoperative views of two cases that required resection of ipsilateral kidney & colon with the postoperative specimens below.

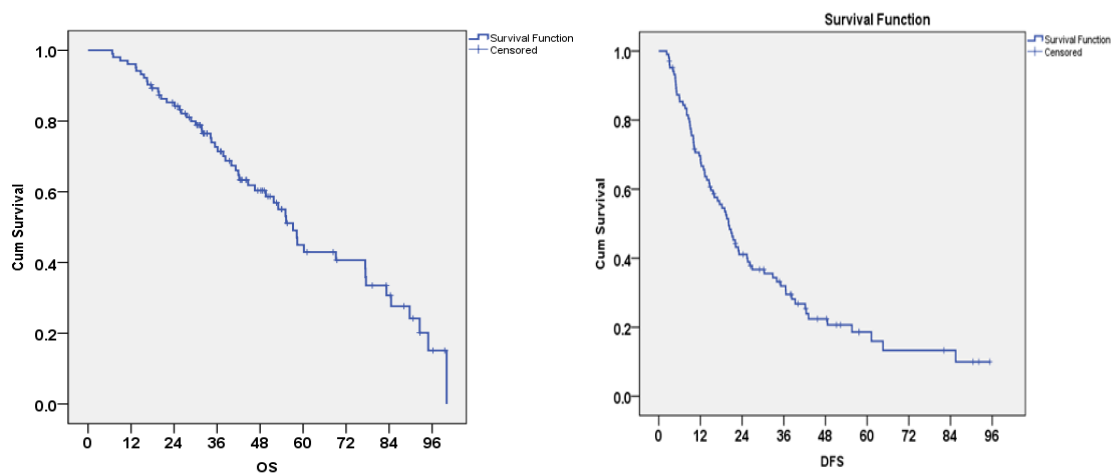


Figure 3 OS curve (left) & DFS curve (right)

Ballo et al, (2007) found that beside poor up to no response to RT, significant morbidities result (autonomic, sensory or motor neuropathies, ischemic bladder or ureteric injury with urinary fistula, intestinal adhesions with subacute or chronic bowel obstruction, ischemic bowel injury with fecal fistula). Also, RT administration to retroperitoneum carries a challenge to the

radiotherapist from the large field size & presence of vital viscera (liver, kidneys, spinal cord & small or large bowels). In our work, RT was given to (37 cases, 71.1%) & showed only border line OS improvement compared to those (15 cases, 28.8%) who did not (52.6% versus 21.4% at 5 years; $p=0.071$ respectively). No similar influence for RT was obtained on DFS (Ballo et al., 2007). Again, few studies clarified survival benefits from administration of CTH, besides it may worsen patient's performance status before or after surgeries. Its main indications are still for high grade types; non R0 resection & recurrent unresectable tumors. In our work, CTH was given to (38 cases, 73%) with borderline OS improvement among those received CTH versus those who did not (43.7% versus 40.5% at 5 years; $p=0.097$) respectively. All cases received Adriamycin -Ifosfamide regimen for 3-6 cycles. However, significant DFS benefit was obtained among those received CTH over those who did not (19.1% versus 6.7% at 5 years; $p=0.02$ respectively) although this similar influence was not obtained on OS (Jones et al., 2005).

Clear surgical margins depend mainly on adherence to nearby viscera & major vessels. Achieving complete resection varies in studies from 44% to 96%. Rates worsen with recurrent cases. For negative margin to be achieved, combined resection of more than one organ abutted, displaced but not infiltrated (kidneys, bowel, adrenal gland, pancreas & spleen) is needed rather than peeling off tumor from these organs. Despite this, it is not performed in most patients as morbidity from these organs absence may not be compatible with life. Moreover, large sized RPLS usually abuts or enchases inferior vena cava, abdominal aorta, common iliac arteries & veins or ureters where the peeling off maneuver is the only way for resection to save such important structures. In our work, clear surgical margins obtained in (31 cases, 59.6%). Nearby organ resection needed in (35 cases 67.3%) with the kidney being commonest organ resected (29 cases, 55.7%) (Gholami et al., 2010; Kumar et al., 2012).

Well differentiated RPLS grows slowly while undifferentiated type has rapid growth rate with higher potential for systemic failure. Therefore, it is expected that well differentiated type shows better outcome concerning DFS & OS. With repeated recurrences, well differentiated RPLS may convert to undifferentiated type invading nearby structures (abdominal aorta, inferior vena cava, ureters). Hence, the peeling off now may not be feasible with an extremely surgical challenge than the 1ry undifferentiated RPLS resections. Singer et al, (2003) & Neuhaus et al, (2005) published their largest series on RPLS, concluded that 5-years OS for well differentiated types is nearly 90%, while 5-years OS for pleomorphic types is only 30-50%. Undifferentiated & myxoid/round cell types have intermediate 5-years OS rates of 75% & 60-90% respectively (Singer et al., 2003; Neuhaus et al., 2005; Lee et al., 2011).

In our study, well differentiated type was the commonest encountered (31 cases, 59.6%) with 27 cases (51.9%) classified as grade I, (8 cases, 15.3%) as grade II while high grade tumors were found in (17 cases, 32.6%). Our analysis showed that well differentiated type was associated with better OS than myxoid/round cell, undifferentiated & pleomorphic types respectively (29% versus 27% versus 16% versus 7% at 5 years; $p=0.09$). Moreover, DFS rates showed improvement with well differentiated type over myxoid/round cell, undifferentiated & pleomorphic types (43.3% versus 32.5%, versus 12.5%, versus 10.8 at 3 years respectively; $p=0.038$).

Tumors usually recur after surgery. Local & systemic failure after surgery approached 50%-85% in most studies. Recurrences usually attain large sizes. Although this, debulking surgeries still is justified as the only modality, that carries a chance for control. Adequate recurrence resection improves both DFS & OS rates. Metastectomy could be offered in oligometastatic single organ disease following long period of complete remission after primary disease control. Again, we can consider low dose RT or CTH on palliative basis to improve quality of life. They are given mainly for cases with disease failure (local or systemic) with good performance that cannot be resected safely & completely (Pisters et al., 2003; Gronchi et al., 2004; Mendenhall et al., 2005).

Our analysis showed disease failure occurred in (35 cases, 67.3%); 8 cases (15.3%) locally, 17 cases (32.6%) systemic & 10 cases (28.8%) with both. Local control rates at 1, 3 & 5 years were 68.7%, 30.8% & 17% respectively while distant metastasis free survival rates at 1, 3 & 5 years were 96.2%, 72.4% & 43.9% respectively. Time to local failure ranged (2.97-96.33 months), with median of 43.3 months, while time to distant failure ranged (2.28-98.96 months) with median (32.6 months). Systemic failure occurred mainly in lungs (28 cases, 53.8%).

5. CONCLUSION

Surgery is the cornerstone for treatment of RPLS treatment. It should be aggressive from start with En-bloc organ resection whenever feasible. Morbidities are expected with recurrent surgeries due to multiple organ resections. RT & CTH have limited role except in high grade; non R0 resection; recurrent & metastatic disease. Poor prognosis expected with grade III, undifferentiation, advanced stage, sizes >20cm & +ve margins. Further studies are needed to address novel targeted therapies, new CTH protocols & intensity modulated RT techniques for outcome improvement.

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Author's contributions

All authors shared equal parts during the release of this article concerning data collection, statistical work, writing different parts of the article including methodology, results & discussion.

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Conflict of Interest

Authors declare that there are no conflicts of interest.

Informed consent

Written & Oral informed consent was obtained from all individual participants included in the study. Additional informed consent was obtained from all individual participants for whom identifying information is included in this manuscript.

Ethical Approval

This Study was approved by the Medical Ethical Committee (Institutional Review Board-IRB) of The National Cancer Institute/Cairo University. Approved on Wednesday 21 December 2016; IRB number 09-2016-917.

Data and materials availability

All data associated with this study are present in the paper.

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